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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,473	10/30/2003	Sham Chopra	0056987-000004	7427
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			ART UNIT 1614	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/697,473

Applicant(s)

CHOPRA, SHAM

Examiner

James D. Anderson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 April 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-28 is/are rejected.
- 7) ☒ Claim(s) 1 and 24 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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CLAIMS 1-28 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 4/30/2007 has been received and entered into the application. Accordingly, claims 1-2, 5, 13, 18-19, 21, 24 and 26 have been amended.

In view of the above amendments, the objection to claim 12 has been overcome and thus is withdrawn. Also, the amendments and Applicants' remarks have overcome the rejections not reiterated herein from the previous Office Action. Such rejections are hereby withdrawn. The following rejections are either reiterated or newly applied and constitute the totality of issues remaining in the present application.

Response to Arguments

Applicant's arguments filed 4/30/2007 have been fully considered but they fail to persuade the Examiner of an error in his determination that the instantly claimed invention is obvious over Conte *et al.* in view of the cited references.

Firstly, Applicant argues that chronotherapy tablets of the present invention are provided which comprise a coating which envelops the core and at least one exposed release face substantially perpendicular to the longitudinal axis of the core. Applicant goes on to assert that this claim language means that the release face is "flat and circular and flush with the coat". However, there is nothing in the claim language to suggest that the release face must be "flush with the coat". The coating, as claimed, "envelop[s] the core, except for, at least one exposed release face of the core". Thus, the instant claim language allows for a protruding section of the core, just as in the tablets disclosed in Conte *et al.*

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Secondly, Applicant argues that the tablets of the present invention are capable of providing several pulses of drug delivery, thereby further distinguishing them from the tablets disclosed in Conte *et al.* However, Conte *et al.* specifically contemplate such drug delivery. For example, the first line of the abstract states that the invention is “[A] tablet for pharmaceutical use able to release active substances at successive times...” The reference thus suggests several pulses of drug can be released over time.

Thirdly, Applicant argues that the instantly claimed coating which envelops the core, as amended, comprises water-soluble pore-forming material(s) that substantially leach out of the coat thereby introducing mechanical instability. The coat “remains intact throughout the delivery period but disintegrates prior to evacuation from the colon”. However, Conte *et al.* also suggest and motivate such a coating wherein they state, “[W]ater-insoluble polymers are preferably used, but in certain embodiments polymers soluble in an alkaline environment can be used to facilitate destruction of the casing when in the enteric tract” (col. 3, lines 57-60).

Fourthly, Applicant argues that amendments to claim 5, wherein the tablet comprises two exposed release faces of the core wherein one release is at one end of the core and the second release face is at the second end of the core, are not contemplated or suggested by Conte *et al.* in combination with any of the cited references. This argument is not persuasive because modifying the tablet disclosed in Conte *et al.* so as to provide two release faces would have been *prima facie* obvious at the time of the invention. Such a modification allows a drug to be released simultaneously from both ends of the core, as opposed to release from only one end. In effect, this simultaneous release allows for more active agent(s) to be released in a shorter period of time (*i.e.*, the release rate of a drug or drugs is increased). Conte *et al.* suggest and motivate

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such a modification of active agent release profiles. For example, the rate of gelling and/or solubilization of the barrier layer and/or of the casing is the factor that controls the release of the second portion of active substance (col. 2, lines 57-60). As such, if the casing is removed from a second end of the tablet, the release of the second active substance will be increased or released at the same rate as the first active substance from the first end of the tablet.

Claim Objections

Claims 1 and 24 are objected to because of the following informalities: the word "cylindrical" is misspelled. The correct spelling is ---cylindrical---. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-17 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over Conte *et al.* (U.S. Patent No. 4,865,849; Issued Sep. 12, 1989) (cited by Applicant).

The instant claims are drawn to a tablet comprised of a cylindrical core having at least two superposed layers of different compositions and wherein a coating envelops the core except for at least one exposed release face of the core at least one end of the core. Instant claim 9 recites a multilayer tablet wherein the first layer is a delay layer. Claim 13 recites a tablet according to claim 9 comprising additional layers of active ingredient. Claims 14-16 recite a tablet comprising the drug naproxen.

Conte *et al.* disclose a tablet for pharmaceutical use able to release active substances at successive times, comprising a first layer containing a portion of active substance, a barrier layer which is interposed between the first layer and a third layer containing the remaining portion of active substance (Abstract). Said barrier layer and third layer are housed in a casing, thereby allowing the part of active substance not inserted into the casing to be immediately available for dissolving (*id.*).

The differences between the tablets of Conte *et al.* and that instantly claimed tablets lie in the shape of the tablet and the relative orientation of the layers. Conte *et al.* disclose a spherical tablet wherein the superposed layers are parallel to the longitudinal axis of the tablet, whereas the instantly claimed tablets comprise a cylindrical core having a longitudinal axis wherein the superposed layers are perpendicular to the longitudinal axis. However, such changes in tablet shape and the orientation of the superposed layers are not patentable over Conte *et al.* For example, in *Gardner v. TEC Systems, Inc.*, 725 F.2d 1338, 220 USPQ 777 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 830, 225 USPQ 232 (1984) the Federal Circuit held that, where the only difference between the prior art and the claims was a recitation of relative dimensions of the claimed device and a device having the claimed relative dimensions would not perform differently than the prior art device, the claimed device was not patentably distinct from the prior art device. Similarly, in *In re Dailey*, 357 F.2d 669, 149 USPQ 47 (CCPA 1966), the court held that the configuration of the claimed disposable plastic nursing container was a matter of choice which a person of ordinary skill in the art would have found obvious absent persuasive evidence that the particular configuration of the claimed container was significant. In the instant case, changing the shape of the spherical tablet disclosed in Conte *et al.* would have been an obvious

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modification because such a modification would not be expected to alter the characteristics of the disclosed tablets.

With respect to instant claims 4, 6, 9-10, 12 and 17 Conte *et al.* teach that the tablet can consist of more than two deposits of active substance separated from each other by layers of polymeric material (*i.e.* barrier or delay layers) (col. 2, lines 11-19; Claim 6). The reference further teaches that the active substance can be of the same or different types in the various deposits of active material (*id.* and Claims 7 and 8). Conte *et al.* explicitly teach tablets comprising ibuprofen (Example 1), propranolol HCl (Example 2), indomethacin (Example 3) and naproxen (Example 4) as the active ingredients therein.

With respect to claim 9, Conte *et al.* disclose that the tablet taught therein can consist of more than two deposits (*i.e.* layers) of active substance separated from each other by layers of polymer material (*i.e.* delay or barrier layers) (col. 2, lines 11-19; Claim 6). Further, the active substance can be in the form of a single layer separated from the external environment by a layer of gellable and/or soluble polymer material (*id.*). As such, it would have been *prima facie* obvious to modify the tablet of Conte *et al.* to form a tablet comprising a first layer that is a delay layer (claim 9) and additional layers comprising active substance. With respect to claim 13, the reference discloses tablets comprising the instantly claimed drugs (see Examples). The reference further discloses tablets with multiple layers of active substances separated by one or more barrier layers. As such, it would have been *prima facie* obvious to formulate a multilayer tablet with a first layer that is a delay layer and subsequent layers containing active substances. This is especially true given that the reference explicitly contemplates a tablet wherein the active substances are separated from the external environment by a barrier layer (col. 2, lines 11-19).

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With respect the instantly claimed limitation wherein the delay layers provide for substantially complete dissolution of the delay layer between about 5 to about 9 hours (*e.g.* claims 13 and 17), the reference utilizes identical polymers to form the barrier layer as the instantly claimed tablets. For example, Applicant describes “dissolution rate modifiers” that include hydroxypropylmethylcellulose (page 17, lines 25-28). Conte *et al.* teach that the barrier layer of their tablets comprises hydroxypropylmethylcellulose (col. 4, lines 33-45). Conte *et al.* further teach that the water penetrates the barrier layer at a rate controlled by the components of the barrier layer itself (col. 2, lines 30-33). The reference further discloses that the time for the barrier layer to be traversed by water is controlled not only by the composition but also by the thickness of the barrier (*id.* at lines 34-36). Thus, Conte *et al.* suggest that the dissolution rate of the barrier layer can be adjusted by changing its composition or thickness. For example, in the tablets exemplified in the reference, the barrier layer becomes progressively permeable to the disintegration liquid, to enable water, after a time of about 0.5 to 1 hours, to come into contact with the second layer of the system (col. 5, lines 42-46). It would have been *prima facie* obvious that adjusting the composition or thickness of the barrier layer would lead to an increased dissolution time of said barrier layer. Further, the Examiner notes that the limitation “between about 5 to about 9 hours” is very broad. As such, it could be interpreted to include the about 1 hour dissolution time disclosed in Conte *et al.*

With respect to claims 14-16, Conte *et al.* disclose a tablet comprising naproxen in a dose of 275 mg per layer (Example 4). Naproxen is “releasable” in about 15 minutes as instantly claimed (*e.g.*, 78% in 10 minutes and 88% in 15 minutes) (col. 12, lines 50-60). With respect to the third layer of naproxen being released as a constant rate over a period of about 5 hours,

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modifying the formulation of naproxen in said third layer would have been well within the level of ordinary skill in the art. It is noted that the prior art discloses various methods of modifying the release rate of drugs from pharmaceutical compositions. For example, Conte *et al.* specifically disclose that the rate of release of active substance from the layers containing it can be varied according to therapeutic needs by varying the composition of the layer concerned (col. 2, lines 61-64). For example, polymers, such as hydroxypropylmethylcellulose, can be added to the active drug layer to effect differing dissolution and release rate profiles (col. 3, lines 4-11). As such, Applicant's instantly claimed release profile amounts to routine optimization of the prior art compositions. The motivation to modify the reference compositions to attain specific release rates of active substances is found in Conte *et al.* wherein they disclose that the rate of release of active substance can be modified to effect differing dissolution and release rate profiles.

Claims 18-20, 24-25 and 27 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over Conte *et al.* (U.S. Patent No. 4,865,849) (cited by applicants) in view of Geoghegan *et al.* (U.S. Patent No. 5,219,621; Issued Jun. 15, 1993).

Conte *et al.* disclose as discussed *supra*. The reference does not explicitly disclose a multilayer tablet formulation comprising the drug diltiazem.

However, Geoghegan *et al.* is provided as evidence that diltiazem is often formulated in a tablet dosage unit and further provides evidence that sustained release of diltiazem is advantageous. The reference discloses that diltiazem is a benzothiazine derivative possessing calcium antagonist activity (col. 1, lines 18-21). It is further disclosed that diltiazem has been

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shown to be useful in alleviating symptoms of chronic heart disease, particularly angina pectoris and myocardial ischemia and hypertension (*id.* at lines 21-27). Diltiazem is conventionally administered in tablet form (30 mg and 60 mg) as diltiazem HCl (*id.* at lines 27-29). Geoghegan *et al.* disclose a diltiazem pellet formulation for oral administration comprising a diltiazem core with a multi-layer membrane surrounding the core (Abstract). The number of layers in the membrane and the ratio of polymers are effective to permit release of diltiazem over an extended period of time (col. 2, lines 42-55). Diltiazem was administered to patients in a dose of 120 mg and reference diltiazem tablets at a dose of 60 mg (col. 12, lines 43-50).

With respect to the instantly claimed doses of diltiazem, the limitations “between about 25 mg – 100 mg” (claim 19), “between about 50 mg – 150 mg” (claim 20) and “between about 80 mg – 200 mg” (claim 21) are rendered obvious by the doses of 60 mg and 120 mg diltiazem that were administered to patients in Geoghegan *et al.*

With respect to the methods recited in instant claims 24-25 and 27, it is well known in the art that diltiazem is useful in the treatment of cardiovascular disease as evidenced in Geoghegan *et al.* As such, because the treatment of cardiovascular disease with diltiazem was well known in the art, it would therefore have been *prima facie* obvious at the time of the invention to use the instantly claimed dosage forms of diltiazem to treat cardiovascular disease.

Thus, it would have been *prima facie* obvious at the time the invention was made to formulate a multi-layer tablet as disclosed in Conte *et al.* with the drug diltiazem and use said tablet to treat a patient with cardiovascular disease. Geoghegan *et al.* provide evidence that diltiazem dosage units were known in the art and useful in the treatment of cardiovascular disease. As such, the skilled artisan would have been imbued with at least a reasonable

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expectation that diltiazem could be used in the multi-layer tablet disclosed in Conte *et al.* The substitution of one drug for another in a prior art drug formulation would have been *prima facie* obvious to the skilled artisan.

Claims 24-26 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over Conte *et al.* (U.S. Patent No. 4,865,849) (cited by applicants) in view of Dunn *et al.* (U.S. Patent No. 4,525,345; Issued Jun. 25, 1985).

Conte *et al.* disclose as discussed *supra*. The reference does not explicitly disclose a method of treating arthritis.

However, Dunn *et al.* disclose a constant rate indomethacin formulation comprising 50 to 200 mg indomethacin (Abstract). Indomethacin, naproxen, and ibuprofen are recited as treatments of choice for arthritic patients (col. 1, lines 23-26). The reference further discloses a method of treating arthritis comprising administering an oral dosage form of indomethacin to a patient (claim 25).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the indomethacin multi-layer tablet disclosed in Conte *et al.* to a patient suffering from arthritis. The skilled artisan would be motivated to do so because indomethacin is an art recognized treatment for arthritis as disclosed in Dunn *et al.* As such, the skilled artisan would have been imbued with at least a reasonable expectation that administration of a multi-layer indomethacin tablet to a patient suffering from arthritis would be an effective treatment.

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Claims 21-25 and 28 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over Conte *et al.* (U.S. Patent No. 4,865,849) (cited by applicants) in view of Le Roux *et al.* (Respiration, 1991, vol. 58, pages 192-197).

Conte *et al.* disclose as discussed *supra*. The reference does not explicitly disclose a multilayer tablet formulation comprising the drug salbutamol or a method of treating asthma.

However, Le Roux *et al.* is provided as evidence that the instantly claimed doses and method of treating asthma with salbutamol were known in the art. Le Roux *et al.* disclose that a slow-release oral formulation of salbutamol (standard oral dose of 4 mg) was administered to asthma patients (Abstract). An 8 mg slow-release oral formulation of salbutamol was also administered to asthma patients (*id.*). It is noted that the 8 mg dose of oral salbutamol was more effective than the 4 mg dose.

With respect to the instantly claimed dose of salbutamol, the limitations “between about 2 mg to about 4 mg” (claim 23) are rendered obvious by the doses of 4 mg and 8 mg salbutamol that were administered to patients in Le Roux *et al.* Le Roux *et al.* also provide further motivation to administer a multi-layer tablet of salbutamol because they disclose that an oral dose of 8 mg was more effective than an oral dose of 4 mg. As such, the skilled artisan would have been motivated to administer salbutamol in a dosage form that would lead to multi-phase release profile of the drug.

With respect to the methods recited in claims 24-25 and 28, it is well known in the art that salbutamol is useful in the treatment of asthma. As such, it would have been *prima facie* obvious at the time of the invention to use the instantly claimed dosage forms of salbutamol to treat asthma.

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Thus, it would have been *prima facie* obvious at the time the invention was made to formulate a multi-layer tablet as disclosed in Conte *et al.* with the drug salbutamol and use said tablet to treat patients with asthma. Le Roux *et al.* provide evidence that oral salbutamol dosage forms were known in the art and used to treat asthma patients. As such, the skilled artisan would have been imbued with at least a reasonable expectation that salbutamol could be used in the multi-layer tablet disclosed in Conte *et al.* The substitution of one drug for another in a prior art drug formulation would have been *prima facie* obvious to the skilled artisan.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.


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Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038.

The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


James D. Anderson
Patent Examiner
AU 1614

July 6, 2007


PHYLLIS SPIVACK
PRIMARY EXAMINER
7/6/07